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14. ABSTRACT
This is the final progress report for ``Mathematical Imaging and Modeling of Cortical Spreading Depression and Wound Healing." The research conducted under this grant represents advances made in image analysis, front tracking, modeling cortical spreading depressions waves in excitable media, and inverse problem theory. It has resulted in nine published papers and two submitted manuscripts

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Report Title

Final Report: Mathematical Imaging and Modeling of Cortical Spreading Depression and Wound Healing

ABSTRACT

This is the final progress report for ``Mathematical Imaging and Modeling of Cortical Spreading Depression and Wound Healing.'' The research conducted under this grant represents advances made in image analysis, front tracking, modeling cortical spreading depressions waves in excitable media, and inverse problem theory. It has resulted in nine published papers and two submitted manuscripts.

Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Received		Paper
02/02/2015	8.00	N. Amini, S. Nowroozizadeh, N. Cirineo, S. Henry, T. Chang, T. Chou, A. L. Coleman, J. Caprioli, K. Nouri-Mahdavi. Influence of the Disc-Fovea Angle on Limits of RNFL Variability and Glaucoma Discrimination, Investigative Ophthalmology & Visual Science, (10 2014): 0. doi: 10.1167/iovs.14-14962
02/02/2015	11.00	Joshua C. Chang, Van M. Savage, Tom Chou. A Path-Integral Approach to Bayesian Inference for Inverse Problems Using the Semiclassical Approximation, Journal of Statistical Physics, (08 2014): 0. doi: 10.1007/s10955-014-1059-y
02/02/2015	10.00	Hamid Hosseini, Nariman Nassiri, Parham Azarbod, JoAnn Giaconi, Tom Chou, Joseph Caprioli, Kouros Nouri-Mahdavi. Measurement of the Optic Disc Vertical Tilt Angle With Spectral-Domain Optical Coherence Tomography and Influencing Factors, American Journal of Ophthalmology, (10 2013): 0. doi: 10.1016/j.ajo.2013.05.036
02/02/2015	9.00	S. Nowroozizadeh, N. Cirineo, N. Amini, S. Knipping, T. Chang, T. Chou, J. Caprioli, K. Nouri-Mahdavi. Influence of Correction of Ocular Magnification on Spectral-Domain OCT Retinal Nerve Fiber Layer Measurement Variability and Performance, Investigative Ophthalmology & Visual Science, (04 2014): 0. doi: 10.1167/iovs.14-13880
07/30/2012	5.00	Joshua Chang, K. C. Brennan, Tom Chou. Tracking Monotonically Advancing Boundaries in Image Sequences Using Graph Cuts and Recursive Kernel Shape Priors, IEEE Transactions on Medical Imaging, (05 2012): 1008. doi:
07/30/2012	6.00	Tom Chou, Michael Siegel. A mechanical model of retinal detachment, Physical Biology, (06 2012): 46001. doi:
TOTAL:		**6**

Number of Papers published in peer-reviewed journals:

(b) Papers published in non-peer-reviewed journals (N/A for none)

Received		Paper
10/01/2013	7.00	Josh Chang, Tom Chou. Iterative Graph Cuts for Image Segmentation with a Nonlinear Statistical Shape Prior, Journal of Mathematical Imaging and Vision, (08 2012): 0. doi:
TOTAL:	**1**	

Number of Papers published in non peer-reviewed journals:

(c) Presentations

Number of Presentations: 1.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received	Paper
TOTAL:	

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received	Paper
TOTAL:	

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

(d) Manuscripts

Received		Paper
02/02/2015	12.00	Josh Chang, Pak-Wing Fok, Tom Chou. Simultaneous Bayesian reconstruction of diffusivities and bond potentials using path integrals, PHYSICAL REVIEW X (12 2014)
07/30/2012	3.00	K. C. Brennan, Dongdong He, Joshua Chang, Huaxiong Huang, Robert Miura, Phillip Wilson, Jonathan Wylie. A mathematical model of the metabolic and perfusion effects on cortical spreading depression, Biophysical Journal (07 2012)
07/30/2012	4.00	Tom Chou. The physics of retinal detachment, Physical Review Letters (05 2012)
08/17/2011	1.00	J. Chang, K. Brennan, T. Chou. Tracking monotonically advancing boundaries in image sequences using graph cuts and recursive kernel shape priors , (08 2011)
TOTAL:		**4**

Number of Manuscripts:

Books

Received		Book
TOTAL:		

Received	Book Chapter

TOTAL:

Patents Submitted

Patents Awarded

Awards

Elected to Fellow of the American Physical Society, Nov. 2013

Graduate Students

NAME	PERCENT_SUPPORTED	Discipline
Josh Chang	0.25	
FTE Equivalent:	**0.25**	
Total Number:	**1**	

Names of Post Doctorates

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Names of Faculty Supported

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Names of Under Graduate students supported

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period: 0.00

The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:..... 0.00

The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:..... 0.00

Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):..... 0.00

Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:..... 0.00

The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense 0.00

The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields: 0.00

Names of Personnel receiving masters degrees

NAME
Total Number:

Names of personnel receiving PHDs

NAME
Josh Chang
Total Number: 1

Names of other research staff

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

Technology Transfer

None to report

Final Progress Report: Mathematical Imaging and Modeling of Cortical Spreading Depression and Wound Healing

Tom Chou, UCLA

Foreword

This is the final progress report for "Mathematical Imaging and Modeling of Cortical Spreading Depression and Wound Healing." The research conducted under this grant led to advances in image analysis, modeling cortical spreading depressions waves in excitable media, and inverse problem theory. It has resulted in ten published papers, one accepted publication and two other submitted manuscripts.

In addition to the originally proposed research, new but related directions were developed in the latter stages of this grant. Specific results were obtained for problems involving retinal imaging, Bayesian inference of stochastic processes, and modeling retinal detachment. These results built upon results and techniques developed from investigations undertaken in the earlier part of the grant.

List of Figures

Statement of Problem Studied

The original research problem was to to develop the mathematical tools to track dynamics of wavefronts as observed in cortical spreading depression (CSD). Accurate tracking of the depression front was then be used to inform mathematical modeling of the biophysical and physiological mechanisms that govern CSD. Exploring these problems also led to applying our approach to the modeling of retinal tissue and the imaging of retinal layers. Machine learning approaches developed for front tracking were also extended and adapted for Bayesian inference of simple stochastic processes.

Most Important Results

Improved segmentation algorithms

Our work on imaging and tracking moving fronts of depressed activity across cortical tissue has been published: J. Chang, K. C. Brennan, and T. Chou, "Tracking monotonically advancing boundaries in image sequences using graph cuts and recursive kernel shape priors," *IEEE Transactions on Medical Imaging*, **31**, 1008 - 1020, (2012). In this approach, we exploited ideas Bayesian prediction and Kalman filtering to compute probability distributions for propogating fronts.

We have further extended this method by reformulating an objective function for statistical image segmentation so that faster graph cut methods can be applied. We applied our extended shape prior methods common images as shown in Fig. 1. These results were published: Joshua C. Chang and Tom Chou, "Iterative graph cuts for image segmentation with a nonlinear statistical shape prior," *Journal of Mathematical Imaging and Vision*, **49**, 87-97, (2014).

Mathematical modeling vascular-activity coupling in CSD

A manuscript describing the effects of blood vessel dynamics on CSD activity has been submitted to Biophysical Journal. In the model, vascular diameter was coupled to potassium concentration. Changing vascular diameter affects the flow of oxygenated blood to the tissue, affecting its ATP production rate, and ultimately influencing the dynamics of the recovery of the depressed activity tissue. Figure 2 recapitulates the main results of our investigation:

Modeling Mitosis and Cellular Cortical Lamination

This study provided a simple method for estimation of cell-cycle parameters in the developing cerebellum from gross histological measurements using observed global constraints. It was determined that symmetric in-plane mitoses of cells in the cerebellum are the most important for proper cerebellar foliation. A manuscript by Joshua C. Chang, Mark Leung, Hamza Gokozan, Patrick Gygli, Fay Patsy Catacutan, Catherine Czeisler, and Jos J. Otero has been accepted to *The Journal of Neuropathology and Experimental Neurology*.

Modeling glutamate release and calcium elevation in CSD

In this combined experimental and computational study, we demonstrate why glutamate release during CSD is the best correlate for neuronal compromise by its coupling with calcium dynamics inside neurons. This study resolves the conflict between Grafstein's K-mediated theory of CSD propagation and Van-Harreveld's glutamate-related theory. We characterize three different wave-speed regimes based on the amount of glutamate released. A manuscript on this work has been submitted.

Mathematical models of blister formation

We first studied the problem of retinal detachment, which shares many mechanistic similarities with epithelial blister formation. Our results are summarized in the Fig 3. Our main result the phase diagram that maps out when a retinal detachment is unstable, or is stable and will likely heal. We have begun to generalize this problem in two directions: (1) Developing models for skin blisters, and (2) Developing a more detailed understanding of the tissue attachment condition. A skin blister shares many similarities with retinal blisters, but is simpler because there are no known active fluid pumps and fluid does not pass through an unruptured blister. However, the sub-blister drainage mechanism is more complex, involving the spatial and geometric properties of both capillaries and lymph vessels. Moreover, osmotic pressure from fluid that leaks out of capillaries is expected to influence the ability of lymph vessels to drain. Finally, we wish to develop a more quantitative understanding of the forces attaching dead epithelial at the blister edge. This contact line of a blister will be modeling using plate theory for the thin tissue layer, including the effects of tension and bending rigidity of the detached epithelial layer.

Bayesian and regularized approaches to inverse problems

Finally, new methods for inverse problems were developed. This line of research arose from our work in quantitative neuroimaging. Here, we developed path-integral based methods for reconstructing coefficent functions in PDEs from measured data. This new approach incorporate the data mismatch terms into an "energy" functional. Treating the target functions to be reconstructed as statistical variable themselves, and functionally varying the data-infused energy functional with respect to the target functions, we find maximum likelihood solutions the target functions. However, the energy functional also includes regularization terms reflecting prior knowledge of the expected correlations of the functions to be reconstructed. In this way, we can reconstruct *probability distributions* over the target functions, providing a means for uncertainty quantification. These new results are described in two manunscripts, one is published: J. Chang, V. Savage, and T. Chou, "A path integral approach to Bayesian inference for inverse problems using the semiclassical approach," *Journal of Statistical Physics*, **157**, 582-602, (2014), and the other has been submitted: J. Chang, P.-W. Fok, and T. Chou, "Simultaneous Bayesian reconstruction of diffusivities and bond potentials using path integrals," Submitted to: *Physical Review X*, (2014).

In this second project, we applied our functional Bayesian inverse approach to directed Brownian motion in the context of single-molecule force spectroscopy (SMFS). SMFS is a ubiquitous experimental method used to determine the bond potential of macromolecules or the adhesion potential of macroscopic materials. By repeatedly applying a pulling force and measuring the bond displacement, data in the form of "trajectories" are obtained. These trajectories were then used to simultaneously reconstruct both the bond potential and the bond coordinate mobility. This approach goes beyond the current state-of-the-art that uses work theorems which cannot reconstruct bond coordinate mobilities. Fig. 4 shows the simultaneous reconstruction of a complex, multi-minimum bond potential and the bond mobility. Uncertainty quantification is indicated by the yellow bands. Our regularization method is able to find the right underlying target functions in this ill-posed inverse problem.

Figures

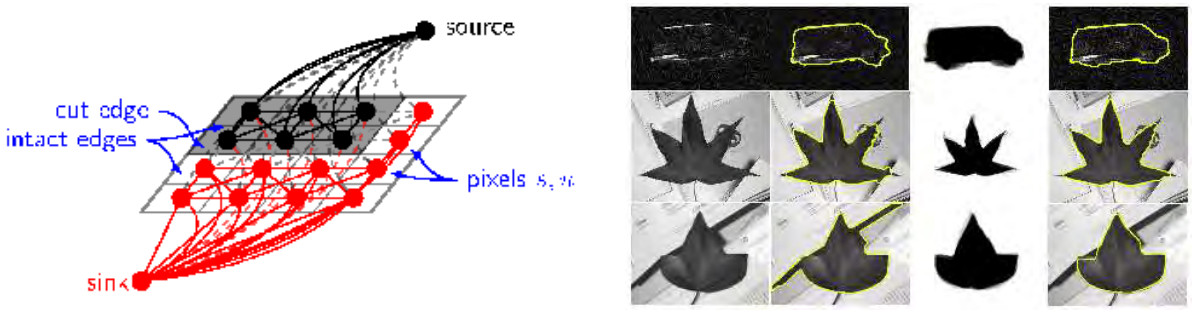

Figure 1: Left: A pixel-by-pixel representation of the graph cuts algorithm for deciding which pixels belong to foreground or background. Segmentation by graph-cuts is computationally more efficient than other methods such as finding level sets. Right: Implementing the graph cuts method into our shape-prior algorithm, we are able to discern objects in the presence confounding backgrounds.

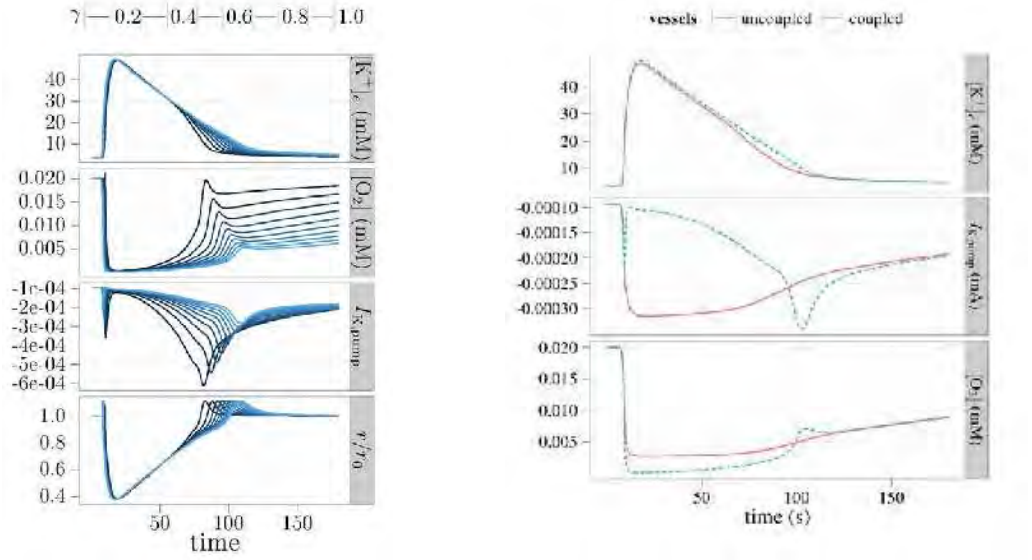

Figure 2: Left: Shown top to bottom are the extracellular potassium level, the cellular oxygen concentration, the potassium ion pump flux, and the typical capillary radius for a typical vascular coupling. Plots are time courses at a fixed position, 780μm downstream of the original stimulus. After a short dilation period, the vessels constrict significantly to about 40% of their rest radii, before recovering. Right: Shown (top to bottom) are the extracellular potassium concentration, the potassium pump flux, and the cellular oxygen level. When vasculature is coupled to extracellular potassium concentration, the extra depletion of oxygen due to supply constraints causes the pump to operate at a slower rate than when vasoconstriction does not occur. As a consequence, the inward potassium flux through the pump is decreased. The result is prolonged recovery time. The vascular coupled model (dashed) is contrasted with the uncoupled problem (solid).

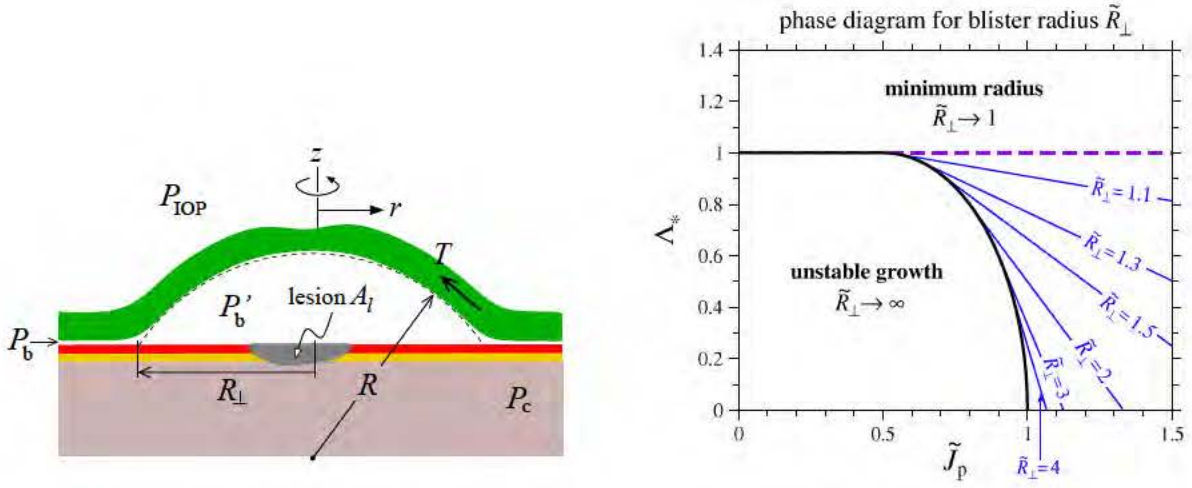

Figure 3: Left: Schematic of a retinal blister. Ingredients in our mechanical model include vascular pressure P_c, subretinal blister pressure P_b', and intraocular pressure P_{IOP}. The retinal tension T is balanced by the various pressures and the fluid flow (not shown) arising from the retinal pigment epithelium (RPE) layer. Right: Results of our model recapitulated in a parameter diagram (the effective RPE pump flux and the effective retinal elasticity. Domain where retinal blister are stable, or unstable to growth or shrinkage, are indicated.

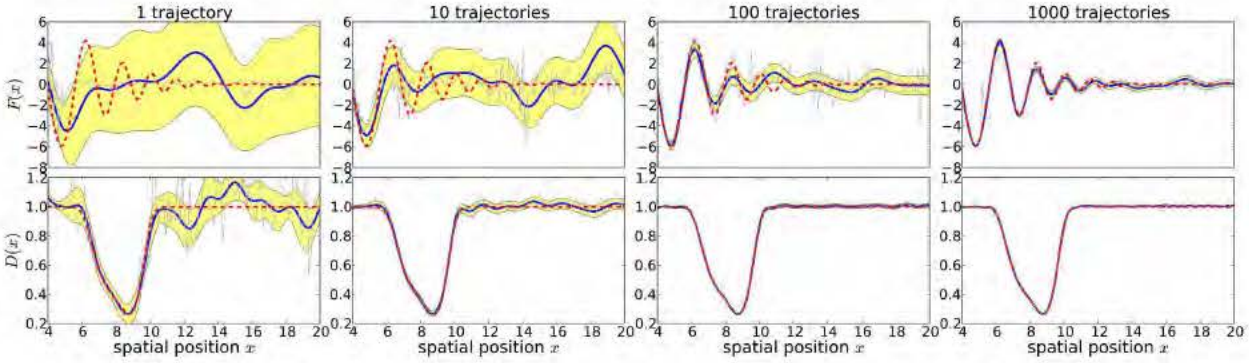

Figure 4: Simultaneous path-integral-baed Bayesian reconstruction of bond potentials and mobilities. The target functions are indicated by the red dashed curves. As more trajectory data is used, the most likely reconstructions approach the ground-truth target functions. Moreover the 95% confidence levels are found through uncertainty quantification.